

Enteric coating of ibuprofen tablets (200 mg) using an aqueous dispersion system

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Ibuprofen is a propionic acid derivative that belongs to the class NSAIDs. Major adverse reactions associated with Ibuprofen are related to GIT and include peptic and mucosal ulcers, dyspepsia, severe gastric pain and bleeding, that results in excessive treatment failure. The goal of this study was to develop enteric coated ibuprofen tablets in order to avoid gastric mucosal irritation, diffusion of drug across mucosal lining and to let active ingredient be absorbed easily in small intestine. The formulation was developed and manufactured through the direct compression process, the simplest, easiest and most economical method of manufacturing. Enteric coating was done using an Opadry white subcoating and an aqueous coating dispersion of Acryl-Eze. Enteric coated formulation was subjected to disintegration and dissolution tests by placing in 0.1 M hydrochloric acid for 2 h and then 1 h in phosphate buffer with a pH of 6.8. About 0.04% of drug was released in the acidic phase and 99.05% in the basic medium. These results reflect that ibuprofen can be successfully enteric coated in order to prevent its release in the stomach and facilitate rapid release of the drug in the duodenum, due to the presence of superdisintegrant. Formulating this enteric coated tablets could increase patient compliance by decreasing adverse drug reactions (ADR_s) associated with Ibuprofen therapy.

Uniterms: Ibuprofen/adverse reactions. Tablets/enteric coating/aqueous dispersion system. Acryl-Eze. Opadry White. Superdisintegrant.

Ibuprofeno é um derivado do ácido propiônico, que pertence à classe dos fármacos não-esteróides (AINES). As principais reações adversas associadas com o ibuprofeno se referem àquelas do trato gastrointestinal (TGI), como úlceras pépticas e da mucosa, dispepsia, dor gástrica grave e sangramento, que resultam em muitas falhas de tratamento. O objetivo do estudo foi desenvolver comprimidos revestidos de ibuprofeno que impeçam a irritação da mucosa gástrica, difusão do fármaco através da mucosa e permitam, facilmente, a absorção do princípio ativo do intestino delgado. A formulação foi desenvolvida e manufaturada por meio de processo de compressão direta, método mais simples e econômico de preparação. O revestimento entérico foi efetuado utilizando-se subrevestimento com Opadry branco e revestimento por dispersão aquosa de Acryl-Eze. A formulação de revestimento para liberação entérica foi submetida a testes de desintegração e de dissolução, em ácido clorídrico 0,1 M, por 2 h, e, então, a 1 h, em tampão fosfato pH 6,8. Cerca de 0,04% do fármaco foi liberado na fase ácida e 99,05%, no meio básico. Estes resultados refletem o fato de que o ibuprofeno pode ser revestido com sucesso, a fim de impedir sua liberação no estômago e facilitar a rápida liberação do fármaco no duodeno, devido à presença de superdesintegrante. A formulação de tais comprimidos aumentaria a adesão do paciente pela diminuição das reações adversas (RAs), associadas à terapia com ibuprofeno.

Unitermos: Ibuprofeno/reações adversas. Comprimidos/revestimento entérico/sistema de dispersão aquosa. Acryl-Eze. Opadry Branco. Superdesintegrante.

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INTRODUCTION

The application of coatings to the surface of pharmaceutical solid-dosage forms, especially tablets, has been practiced for over 150 years (Porter, Bruno, 1990). A significant proportion of pharmaceutical solid dosage forms are coated to give an esthetic touch and to control the bioavailability of the drug (Porter, 2000). Film coating is a technique widely used in the pharmaceutical field to improve and modify technological and release characteristics of capsules, tablets and granules due to the capability of depositing a variety of coating materials onto solid cores (Bonacucina *et al.*, 2006; Fitzgerald, Cole, Taday, 2005; Nastruzzi *et al.*, 2000; Cole *et al.*, 2002; Bobmeir, 1997). The particles prepared by film-coating show the best stability (Wieland-Berghausen *et al.*, 2002). Tablet size, shape and coating are pharmaceutical parameters which can be controlled to minimize esophageal contact of a dosage form with esophageal tissue (Perkins *et al.*, 2001). For instance, enteric coating of acetyl salicylic acid tablets is desirable for preventing stomach upset or irritation in patients taking daily doses (Cunningham, Kinsey, Scattergood, 2001).

Enteric polymers have been shown to be safe, and widely accepted for use in drug products (Biju *et al.*, 2004; Nykanen, 2003). These polymers are insoluble at low pH but dissolve at a pH around or below 7 (Peeters, Kinget, 1993; Bauer, Kesselhut, 1995; Hogan, 1995). A number of coating polymers are available commercially. Shellac is a natural enteric polymer which results in good gastric resistance; however, it often dissolves too slowly in intestinal fluids (Pearnchob, Dashevsky, Bodmeir, 2004). Hydroxypropyl methylcellulose (HPMC) was selected as a base polymer to develop novel enteric coating agents for acid protection, in contrast to ethyl cellulose (EC), it is water soluble and might leach out of the film coating, creating water filled pores through which drug diffuses more rapidly than EC (Kokubo *et al.*, 1997; Gunder, Lippold, Lippold, 1995). Acryl-Eze is a pre-mixed excipient blend based on a methacrylic acid copolymer that is optimized for film-coating applications (Young *et al.*, 2005).

A continuing trend in pharmaceutical coating technology is to use water instead of organic solvents as coating vehicles to minimize environmental and safety hazards. Several aqueous enteric coating systems have been developed and are commercially available (Yuan, Clipse, Wu, 2003). Aqueous-based coating systems are advantageous over organic solvents because they overcome the drawbacks of the latter, namely pollution, explosion hazards and solvent toxicity, especially for operators. For these reasons, water-based systems are now gradually

being applied instead of organic coating systems (Baudoux, Dechesne, Delattre, 1990). The coating material is added as an aqueous solution or dispersion and the excess liquid phase must then be removed, usually by hot air (Lund, 1994). Although aqueous enteric coating systems were an advance on traditional solvent systems, they require separate addition of plasticizers, detackifiers, pigments and other process aids (Lechmann, 1982). Multiple, time-consuming steps are required in the preparation of these aqueous enteric coating dispersions. In addition, many of these systems are provided as liquid dispersions, which can be problematic when handling, transporting and controlling storage conditions (Cunningham, Fegley, 2001).

The model drug is ibuprofen, a widely used NSAIDs. It is an analgesic, anti-inflammatory and anti-pyretic agent (Nazu, 1978; Wood *et al.*, 2006; Potthast *et al.*, 2005). NSAIDs are a group of unrelated organic acids that mostly affect GIT. Dyspeptic complaints (Hollenz, Labenz, 2004), upper GI bleeding (Blot *et al.*, 2004) and mucosal and duodenal ulcers (Davis, 1999; Rang, Dale, Ritter, 2003; Ross, DeHoratius, 1990) are common ADRs associated with this group and may be life threatening (Motola *et al.*, 2004). In 2002, Aletaha found that about 72% of the patients with rheumatoid arthritis treated with NSAIDs received GI-protective therapy mainly with histamine antagonists and sucralfate (Aletaha, Smolen, 2002). Due to GI side effects, the health and economic burdens related to these drugs are considerable (Schwappach, Koeck, 2003). A distinct relationship between effects and side effects exists, namely, rapid absorption beginning in the stomach is associated with intensive gastric-duodenal irritation and ulceration (Brune, Beck, 1991). Epidemiological studies have clearly demonstrated a rank order of risk of ulcer complications for commonly used NSAIDs, with ibuprofen consistently associated with the lowest risk, and piroxicam with the highest (Wolfe, 2003; Langman, 2003).

The aim of current investigation was to develop enteric coated ibuprofen tablets (200 mg) using an aqueous Opadry/Acryl-Eze system, resulting in protection against gastric ADRs. This study evaluated both systems for ease of use and acid resistance. Stability of coated tablets was determined at room and under accelerated conditions.

MATERIALS AND METHOD

Materials

Pure Ibuprofen pure was donated by Deluxe Pharma, Pakistan, Microcrystalline Cellulose (Avicel PH-101; FMC Corporation, USA), Crospovidone (ISP Techno-

TABLE I - Composition of Ibuprofen 200mg tablets (Bushra et al., 2008)

Ingredients (mg/ tablet)	Batch Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ibuprofen	200	200	200	200	200	200	200	200	200
Avicel PH101	150	150	150	175	200	200	200	175	175
Magnesium Stearate	05	7.5	2.5	05	05	05	05	05	05
Crospovidone	10	10	10	10	10	05	2.5	05	2.5
Quantity per Tablet (mg)	365	367.5	362.5	390	415	410	407.5	385	382.5

logies, Inc. Wayne, NJ) and Magnesium Stearate (FMC Corporation, USA) were used as directly compressible excipients. Sodium hydroxide (Merck, Kga A, and Darmstadt, Germany); Monobasic Potassium Phosphate (Merck, Kga A, and Darmstadt, Germany); Methanol HPLC grade (RDH, Sigma-Aldrich GmbH, Seelze, Germany) and all other chemicals used were of analytical grade and obtained from commercial sources. The enteric coating materials were methacrylic acid polymer based pigmented Acryl-Eze (93092157) yellow and the sub coat material was Opadry (YS-1-7027) white, all from Colorcon (Verna, Goa, India).

Packaging materials used for the tablet stability test were polyvinyl chloride (PVC), 218 mm and aluminium foil 206 mm (Zibo Omy Economic and Trading Co. Ltd., China).

Preparation of Tablets

All the ingredients were properly weighed and sieved through a 20 mesh sieve. The blend was compressed using a single punch machine (KORSCH Erweka, No. 7570, Frankfurt, Germany). For optimization, nine different formulations of ibuprofen (200 mg) tablets were developed (Table I) and on the basis of the results obtained from evaluation of different physico-chemical parameters, formulation 6 was selected as an optimized formulation for enteric coating (Bushra *et al.*, 2008).

Enteric Coating of Ibuprofen (200 mg) tablets

• Preparation of Opadry White solution

Compressed tablets were sub coated using Opadry white dispersion. This was prepared by accurately weighing 50g of Opadry white formulated powder while 600 mL of mixture of methyl chloride and ethanol (343 mL of methyl chloride and 257 mL of ethanol) (Cole, 1990) was utilized as the organic solvent, being stirred continuously to form a vortex without drawing air into the liquid. Opadry white coating powder was added steadily to the vortex, avoiding powder flotation on the liquid surface.

This dispersion was thoroughly mixed for 40- 45 minutes in order to obtain a homogenized distribution.

• Preparation of Acryl-Eze Yellow dispersion

320 g of distilled water was weighed into a mixing vessel and stirred to form a vortex. 80 g Acryl-Eze yellow powder was weighed accurately and added to the center of the liquid vortex in a slow steady stream, avoiding clumping and maintaining a vortex. Mixing was continued for around 20 - 25 minutes. Finally Acryl-Eze dispersion was passed through a 250 micron sieve prior to the coating process. Dispersion was continuously stirred during the coating process. Both coating dispersions were prepared according to the technical document and guidelines provided by Colorcon (Colorcon, 2006).

• Coating methodology

Tablet coating was performed in a conventional coating pan (Erweka G.m.b.H., type UG, Frankfurt, Germany) with one spray gun. Table II lists the coating conditions and parameters. Tablet cores were pre-heated to about 40 °C utilizing a dryer and air compressor (Type H-2, No. 311319, Meiji air compressor Mfg. Co. Ltd. Osaka, Japan). The spray gun was filled with Opadry white coating dispersion and operated at a proper flow rate. The pan was set into motion and seal coating solution

TABLE II - Coating Process Parameters

Factors	Conditions
Equipment	12 inch coating pan
Substrate	200-mg Ibuprofen tablets
Pan charge	1 kg
Inlet Temperature	55-65 °C
Bed Temperature	35-40 °C
Distance between spray gun and tablet bed	6 inches
No. of spray guns	1
Pan Speed	12 rpm

was sprayed on to the falling cores under a suitable air pressure (30-35 psi). Upon completion of seal coating, the air heater was switched off and tablets were blow dried for 20-25 minutes in the coating pan. The spray gun was washed thoroughly and filled with prepared Acryl-Eze yellow aqueous dispersion and the same procedure was followed for final coating. The core tablets gained 2% weight during sub coating and about 8-10% weight after Acryl-Eze dispersion. (Table III).

TABLE III - Dispersion Preparation Parameters

Parameters	Sub coat layer	Acryl-Eze
Theoretical weight gain (%)	2	8-10
Dispersion solid content (%)	15	20
Powder (g)	30	80
Organic Solvent (mL)	600	N/A
Deionized Water (g)	N/A	320
Total Dispersion (mL)	630	400

Characterization of coated tablets

• Mechanical strength:

The hardness of the coated tablets was examined by using a tablet hardness tester (Fujiwara, Seisukusho Corporation, Japan). The hardness of 20 randomly selected tablets is shown in Figure 1.

• Disintegration Test

The disintegration test was performed according to

B.P 2004. Six enteric coated tablets were placed in acidic phase consisting of 0.1 M hydrochloric acid. The assembly was operated without the discs for 2 h in a USP basket rack assembly (Erweka ZT-2, Husenstamn). Tablets were removed from solution, dried gently with a paper towel and disintegration was continued in buffer phase for 1 h. Buffer phase was composed of mixed phosphate buffer with a pH of 6.8 that was maintained at 37 ± 2 °C. The assembly was removed and tablets were observed for disintegration.

• Dissolution Test

The dissolution testing of enteric coated formulation was carried out according to USP 27 NF 22 <711>, by adopting Method B (USP convention INC., 2004) in pH 1.2 and pH 6.8 buffers.

The Acid Stage was performed using 1000 mL of 0.1 M hydrochloric acid placed in a USP dissolution bath (Erweka DT 700, Husenstamn, Germany), equilibrated to a temperature of 37 ± 0.5 °C. The paddle stirring rate was set at 50 rpm. Six tablets were introduced into the apparatus and the apparatus was run for 2 h. After the operation outlined above, an aliquot of the fluid was drawn, and the *Buffer Stage* was commenced.

The Buffer Stage consisted of a phosphate buffer of pH 6.8 prepared by mixing 0.1 M hydrochloric acid with 0.20 M tribasic sodium phosphate (3:1). The apparatus was operated for a further 1 h. At the end of the time period, an aliquot of the fluid was drawn. Samples were assayed spectrophotometrically (UV 150-02, Double beam spectrophotometer, Shimadzu Corp., Japan) at 221 nm.

Stability test of coated tablets

Ibuprofen coated tablets were blister packed using a blister packing machine (BQS, H 060125, Pam-Pac Machines Pvt. Ltd.) in 1×10 's using aluminium foil 206 and PVC 218 mm (Zibo Omy Economic and Trading Co.Ltd., China). Stability studies were carried out according to ICH guidelines. Tests were conducted under room temperature (RT) and accelerated stability conditions. The samples designed for RT storage were kept at 30 ± 2 °C and $65 \pm 5\%$ relative humidity (RH) and for accelerated stability were reserved at 40 ± 2 °C and $75 \pm 5\%$ RH, in a humidity chamber (Binder GMBH Bergster, 14D-78532, Tuttingen Germany). The RT samples were pulled from stability and tested 0, 3, 6, 9 and 12 months after the date of packaging. The accelerated stability samples were pulled from stability and tested 0, 1, 2, 3 and 6 months after the date of packaging. Dissolution and assay were performed to evaluate the stability of coated tablets. The percent dissolution and assay of the coated tablets are shown in Tables V and VI.

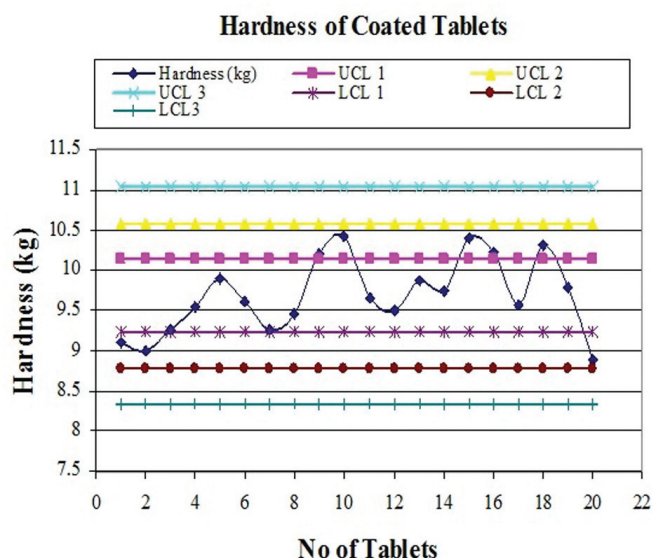


FIGURE 1 - Mechanical strength of coated tablets, with upper and lower control limits.

RESULTS AND DISCUSSION

Controlled and localized release of drugs in the intestine can be achieved by enteric coating. The design of enteric-coated tablets has so far remained empirical, in part because of the lack of a quantitative description of the drug release kinetics (Ozturk *et al.*, 1998; Hosny, El-Mahrouk, Gouda, 1998). The functionality of coatings from aqueous dispersions is linked to coalescence of latex particles. Thus any incomplete film formation, caused by too high or too low coating temperatures, may result in highly permeable coatings (Petereit, Weisbrod, 1999).

The goal of this study was to develop enteric coated ibuprofen tablets. Opadry white coating dispersion was used for sub coating. Enteric coating was successfully done using Acryl-Eze Yellow polymer which is an aqueous dispersion. Tablets were coated smoothly without having any physical visible defects such as orange peel effect, chipping, tacking or other flaws. These two systems are dry, dispersible powders that do not require the use of any additional plasticizer, detackifiers or neutralization agents. During coating, certain parameters require great care such as temperature of coating pan and the spray rate of coating solution. If these are not maintained properly, they affect the smoothness and uniformity of coating. The hardness of 20 coated tablets was measured using a hardness tester and were found to be in accordance with specifications. Tablet hardness is represented graphically with three upper and lower control limits (Figure 1). The efficiency of the coating was determined by subjecting the coated tablets to gastric pH, and drug release was analyzed by a spectrophotometer. Results of disintegration and dissolution are shown in Tables IV and V.

Krogers *et al.*, in 2002, investigated three formulation or process parameters of potential importance, including the plasticizer concentration, the temperature of

coating pan and the spray rate of the coating solution. At low spray rates, the temperature of the coating pan did not affect the roughness of the coated tablets. At higher spray rates, higher temperature gave smoother films. In another study, process variables investigated were inlet airflow, pan speed, inlet air temperature, coating time, atomization pressure, and fan pressure. Pan speed and coating duration were also identified as variables significantly affecting content uniformity (Krogars *et al.*, 2000; Rege, Garmise, 2003). It was shown that lower rates of drug release from the coated tablets may be obtained by using high inlet-air temperature and low spray rate of the polymeric dispersion during coating. Increased temperature for various time periods to remove water and solvent from the product affects the properties of final products (Frisbee, Metha, McGinity, 2002).

Tablets used in a functional coating process must be sufficiently robust to withstand mechanical stresses and should exhibit a very low potential for erosion and edge chipping. Any defect in the tablet core may result in a localized weakness of the functional film. A sub coating process may be used in order to provide a protective coating to the cores, although this step is optional. Subcoating does however prevent interaction between the drug substance and coating polymer. In this study, sub coating was done with Opadry white, resulting in smooth tablets with improved mechanical strength. Acryl-Eze Yellow and Opadry white dispersions are fully formulated polymer systems, whose mixing process consisted of a simple addition of the powder formulations to water. It requires little effort and time. Sieving was done to ensure that no dispersed particles of polymer remained that could result in gun blockages. Both dispersions were stirred during the experiment to avoid sedimentation and coalescence of particles.

Many authors have described different enteric coated formulations using a variety of coating polymers to avoid local gastrointestinal irritation (Debunne, Vervaet, Remon, 2002; Biju *et al.*, 2004; Sinha *et al.*, 2006). In the current study, Crospovidone, a superdisintegrant, was utilized which showed fast *in vitro* drug release and presented better burst effect and rapid drug release compared to traditional disintegrants (Tables IV and V). This approach is especially important because the release of drug is already delayed for 2h, thus by incorporation of Crospovidone the drug will be rapidly released in the duodenum as the polymer coat erodes at high pH 6-7. Tablets showed complete acid resistance for 2 h (Figure 2). Drug release met the criteria outlined in this study i.e. not less than 80% dissolved after 60 minutes in buffer pH 6.8. Although traditional aqueous enteric coating systems can

TABLE IV - Disintegration result of ibuprofen (200 mg) tablets

Media	Result
0.1 M hydrochloric acid	No signs of cracking or softening observed
Phosphate Buffer pH 6.8	Tablet was completely disintegrated in 7-9 minutes.

TABLE V - Dissolution result of ibuprofen (200mg) tablets

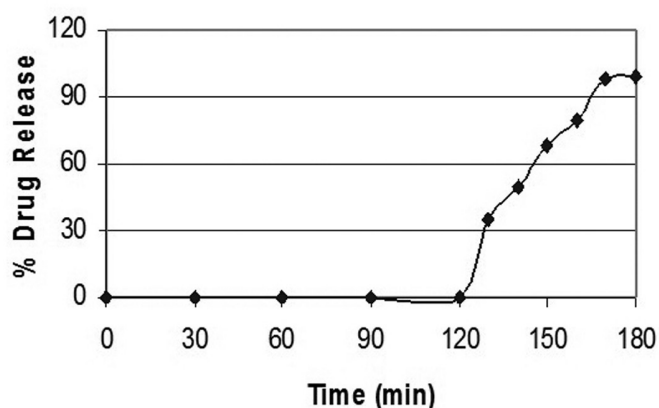
Media	Average Drug Release (%)
0.1 M hydrochloric acid	0.08
Phosphate Buffer pH 6.8	99.05

TABLE VI – Stability testing of Ibuprofen 200mg Tablets at Room Temperature

Batch No	Period (Month)	Physical Characteristics (Faint Yellow Tablet)	%Dissolution Ibuprofen (200 mg/Tab (NLT 80%))	%Assay Ibuprofen (200 mg/Tab) (95-105%)
F6	0	Complies	99.05	100.15
F6	3	Complies	98.95	99.89
F6	6	Complies	98.90	99.56
F6	9	Complies	98.50	99.10
F6	12	Complies	98.25	98.78

TABLE VII - Stability testing of Ibuprofen 200mg Tablets under Accelerated Conditions

Batch No	Period (Month)	Physical Characteristics (Faint Yellow Tablet)	%Dissolution Ibuprofen (200 mg/Tab) (NLT 80%)	%Assay Ibuprofen (200 mg/Tab) (95-105%)
F6	0	Complies	99.05	100.15
F6	1	Complies	98.99	99.95
F6	2	Complies	98.95	99.85
F6	3	Complies	98.65	99.74
F6	6	Complies	98.20	98.56

**FIGURE 2** - Drug Release from Ibuprofen tablets in 0.1 M hydrochloric acid and pH6.8 phosphate buffer.

require multiple component mixing steps before coating, these novel systems were dispersed in only one step in the minimum amount of time, and produced acceptable weight gains. The acrylic-based system offers the additional advantage of being fully pigmented, eliminating the need for additional color application if a colored tablet is desired.

Tablets were stored in a temperature and humidity controlled chamber to observe the stability of the formulation. Results of stability testing were satisfactory, showing no significant variation in physical characteristics, color, hardness or disintegration time of coated tablets. In vitro drug release studies were carried out since these are considered the best tool for assessing *in vivo* drug behavior.

Percent dissolution and assay were within the acceptable limits of USP (Tables VI and VII). All data indicated that the coating layer was essentially unchanged and provided the desirable enteric protection. Coated ibuprofen tablets were stable under stability testing conditions.

CONCLUSION

The intention was to prepare enteric coated ibuprofen tablets (200 mg) using a novel Acryl-Eze yellow enteric polymer and Opadry white aqueous dispersions that prevent drug liberation in the stomach. The coating process for both systems was free of problems and resulted in highly smooth coated colored tablets with no visible defects. Dissolution and disintegration results showed strong acid resistance whereas the drug was freely released in 6.8 buffer solution. The results of stability testing were satisfactory, indicating that coated ibuprofen tablets were stable under the testing conditions.

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